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OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

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Subject: Sensitivity of Neurodevelopmental Tests versus Thyroid Hormone Concentrations

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To: Annie Jarabek
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This is a follow-up to our recent conversation about the differences in sensitivity between measures of thyroid hormones versus developmental neurotoxicity tests. I presented a seminar on this issue at the US EPA/CMA/World Wildlife Fund Sponsored Workshop on Screening Methods for Endocrine Disruptors - Thyroid Function, Duke University (June, 1997). While a synopsis of this meeting is being published (DeVito et al., in press) it does not contain an in depth review of the data that I reviewed for this talk. I have briefly outlined the major finding of my talk below.

The role of thyroid hormones in developing humans and other animals is well documented. Hypothyroidism during development leads to permanent alterations in a number of organ systems including the central nervous system and the male reproductive system. These statements are not widely debated and have been accepted as fact for many decades. What is currently questionable is the sensitivity of animal models used to explore the role of thyroid hormones on neural development. Most of the data collected and published to date involved the use of high dosages of thyrotoxic chemicals (e.g., methimazole, propylthiouracil) or thyroidectomy. These treatments severely depressed circulating concentrations of thyroid hormones. The question remains as to whether any of the currently available tests are capable of detecting smaller or more subtle changes in the development of the nervous system. To address this question, I reviewed a large portion of the available peer-reviewed published data. I included papers which presented measurements of both thyroid hormones and any dependent measure of nervous system development. I have summarized this data in Figure 1.

The data in this figure suggest that measurements of nervous system development are less sensitive than measurements of thyroxine (T4). This may be a number of reasons for this relationship. First, the developing brain may be protected from perturbations in circulating

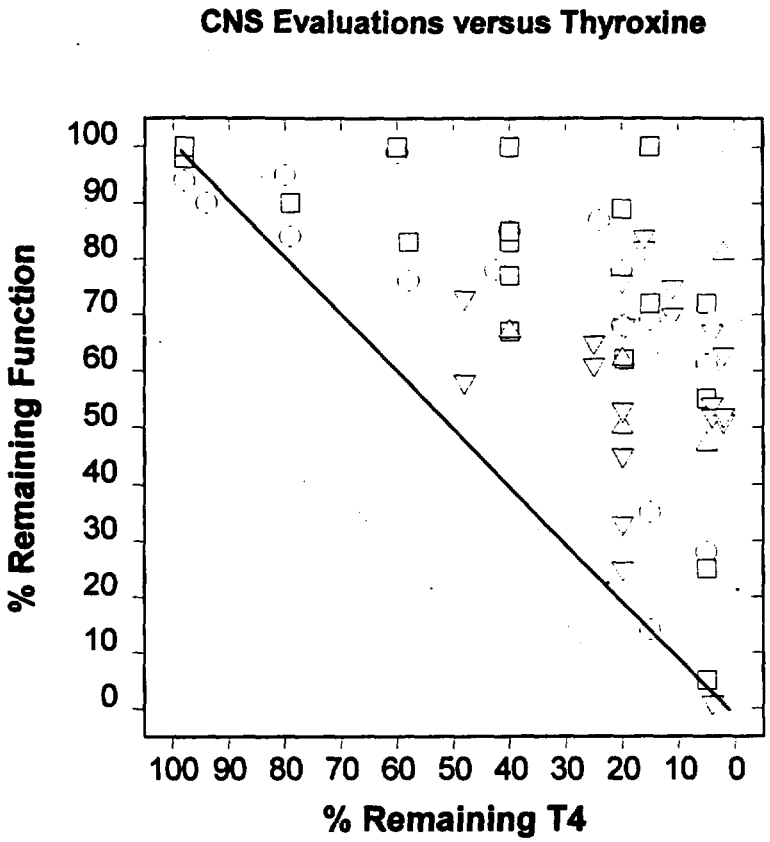

Figure 1. The relationship between tests of nervous system development and circulating total concentrations of thyroxine (T4) to detect the effects of hypothyroxenemia-inducing agents. The y-axis plots the amount of remaining function (or structure) following developmental disruption of thyroid hormones. The x-axis plots the remaining percentage of serum T4. The various symbols represent data from different classes of function (behavioral or biochemical) or structural endpoints. The area below and to the left of the diagonal line represents endpoints that are more sensitive to the chemical insult compared to T4. The area above and to the right of the line represents endpoints that are less sensitive. Notice that most measures of nervous system development are not affected until T4 concentrations are greatly decreased.

concentrations of T4. Evidence in support of this hypothesis can be seen in a paper by Morse et al. (1996). In this paper the authors demonstrated that up regulation of deiodinases in brain tissue compensated for very large decreases in circulating T4. This upregulation (which increases the intracellular conversion of T4 to T3) resulted in no change in brain concentrations of T3. The second, and more worrisome, reason for this relationship is that currently available methods (for detecting changes in nervous system development following disruption of thyroid hormones) are just not very sensitive. Testing this hypothesis is hampered by a lack of good biomarkers for activation of thyroid hormone receptors in developing nervous tissue. Most data published to data have used methods that measure events far downstream (e.g., behavioral functions or morphometric measurements of brain areas) from the initial interaction of T3 with the receptor and subsequent activation of the thyroid response elements. There are a number of laboratories currently developing new methods that may help resolve this issue.

In summary, I urge caution in interpretation of the neurodevelopmental data available in the perchlorate arena. The lack of detectable changes at the higher end of the perchlorate concentration-response curve should not be taken as evidence of a lack of effect. Indeed, the increased size of the corpus callosum and the alteration in the ontogeny of motor activity argue that there are probably changes in the structure and function of the developing nervous system occurring at lower concentrations. One should also remember that the Developmental Neurotoxicity Study was designed as a screening tool. This battery was not intended for use in characterizing the dose-response for chemicals that affect nervous system development via a known mechanism such as hypothyroidism. Indeed, recent data from my laboratory (Goldey et al., 1995a; 1995b) suggest that this battery is fairly insensitive to alterations in thyroid hormones during development.

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